

Novel GCH1 variant in Dopa-responsive dystonia and Parkinson's disease

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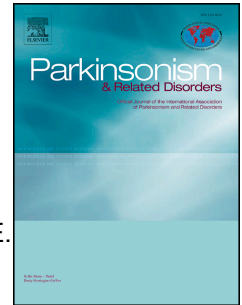
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Novel GCH1 variant in Dopa-responsive dystonia and Parkinson's disease

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Novel *GCH1* variant in Dopa responsive dystonia

Keywords: Parkinson's disease; Dopa responsive dystonia; GCH1; SPECT DAT imaging.

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Abstract**Background**

GTP cyclohydrolase I (*GCHI*) mutations are the commonest cause of Dopa-responsive dystonia (DRD). Clinical phenotypes can be broad, even within a single family.

Methods

We present clinical, genetic and functional imaging data on a British kindred in which affected subjects display phenotypes ranging from DRD to Parkinson's disease (PD). Twelve family members were studied. Clinical examination, dopamine transporter (DAT) imaging, and molecular genetic analysis of *GCHI* and the commonest known familial PD-related genes were performed.

Results

We have identified a novel missense variant, c.5A>G, p.(Glu2Gly), within the *GCHI* gene in affected family members displaying a range of phenotypes.

Two affected subjects carrying this variant had abnormal DAT imaging. These two with abnormal DAT imaging had a PD phenotype, while the remaining three subjects with the novel *GCHI* variant had normal DAT imaging and a DRD phenotype.

Conclusions

We propose that this *GCHI* variant is pathogenic in this family and these findings suggest that similar mechanisms involving abnormal GTP cyclohydrolase I may underlie both PD and DRD. *GCHI* genetic testing should be considered in patients with PD and a family history of DRD.

Introduction

Dopa-responsive dystonia (DRD) is an autosomal dominant dystonia, now classified as DYT5, with an estimated incidence of between 0.5 and 1 per million [1]. DRD typically manifests as lower limb dystonia in childhood, although the spectrum of symptoms can be broad, even within the same family. Patients typically have an excellent and sustained response to low dose levodopa. Women are more commonly affected with a lower penetrance of mutations in men [2, 3].

Mutations in the GTP cyclohydrolase I gene (*GCHI*) are the most common cause of DRD. *GCHI* is located on chromosome 14 (14q22.1-q22.2) and encodes the 32-kDa guanosine 5'-triphosphate cyclohydrolase 1 (GTPCH1) protein. *GCHI* contains six exons, and more than 200 different mutations have been identified [1, 2].

Single positron emission computerised tomography (SPECT) Dopamine Transporter (DAT) imaging is a demonstration of *in vivo* striatal dopamine activity. The DAT ligands for SPECT, including [¹²³I]FP-CIT (DaTSCAN) have all shown significantly reduced striatal uptake in PD [4], whilst uptake has usually been normal in DRD [5].

We have studied a family with an inherited movement disorder, with phenotypes ranging from DRD to slowly progressive PD. We report results from clinical, genetic and imaging studies of this kindred.

Methods

Twelve members of the kindred were studied. A diagnosis of PD was made according to United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank clinical diagnostic criteria. The Hoehn and Yahr PD rating scale and a Folstein MMSE (Mini

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Mental State Examination) were performed on each subject. Olfactory function was assessed by use of the University of Pennsylvania Smell Identification Test (UPSIT-40) (Sensonics, Haddon Heights, NJ) and data compared to normative values. Seven subjects (II:1-II:5, III:1 and III:11) underwent dopamine transporter SPECT scanning (DaTSCAN, Amersham Health) and images reviewed by ER, who was blinded to demographic and clinical data.

Molecular genetic screening of the six affected family members was performed by polymerase chain reaction (PCR) and sequencing of the entire coding sequence, and intron-exon boundaries, of the genes *SNCA*, *Parkin*, *DJ-1*, *PINK1*, *LRRK2* and *GCHI*, using primers and PCR conditions available on request. Multiple ligation-dependent probe amplification (MLPA) was used to detect the presence or absence of copy number variation, using MLPA kits P051 and P052 (MRC Holland), details available on request. Subsequently, six unaffected family members (II:2 and III:4,5,7,9,13) and 150 UK control DNA samples from the PD GEN DNA databank were screened for the novel *GCHI* variant.

All subjects gave informed written consent to take part in the study. The study had appropriate ethical approval from South Birmingham LREC and Sandwell and West Birmingham LREC.

Results

Twelve individuals in the pedigree (figure 1, those annotated with an age) were examined in detail. We noted features consistent with slowly progressive PD in individuals II:1 and II:4 (supplementary video), with additional levodopa-induced dyskinesias and dementia in subject II:1. Disease onset was at 58 and 50 years in II:1 and II:4 respectively. Subject II:3 had an isolated rest tremor (asymmetrical, right

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upper limb), with an older age of onset of 75 years, had not progressed over six years and did not meet diagnostic criteria for PD. Subjects II:5, III:1 and III:11 had features consistent with DRD, with median age of disease onset 17 years and median disease duration of 22 years. The remaining members of the family were unaffected. All the studied subjects are Caucasian and clinical details of affected individuals are summarised in Table 1 (more clinical details in supplementary data).

The findings from DaTSCAN images on six affected subjects (II:1, II:3-II:5, III:1 and III:11) and one unaffected subject (II:2) are summarised in table 1 (supplementary data). Subjects II:3 and II:4 had a second DaTSCAN performed 18 months after the first scan due to atypical disease progression (ie only very slowly progressing which would be unexpected in idiopathic PD).

No novel or previously documented mutations were identified in the coding sequences of *SNCA*, *Parkin*, *PINK1*, *DJ-1* and *LRRK2*. However, a novel heterozygous substitution was identified in the first exon of *GCHI* affecting the fifth nucleotide of the open reading frame (c.5A>G) (supplementary data). This change is predicted to replace a glutamic acid residue with glycine (p.(Glu2Gly)). This mutation (GenBank accession NM_000161.2, NP_000152.1.) is not listed as a known mutation or polymorphism in standard databases (dbSNP138 (<http://www.ncbi.nlm.nih.gov/SNP/>); 1000 genomes (release October 2013, [http://browser.1000genomes.org.](http://browser.1000genomes.org/)); Exome Variant Server (HLBI-EP6500, <http://evs.gs.washington.edu/EVS/> database accessed Sept, 2014). The novel *GCHI* variant was identified in five of the affected members of the family, but not in subject II:3 or unaffected subjects II:2 and III:4,5,7,9,13, nor in 300 UK control chromosomes. MLPA did not reveal any copy number variation in *SNCA*, *Parkin*, *PINK1*, *DJ-1* and *LRRK2* or *GCHI*.

Discussion

We have identified a novel heterozygous missense variant within *GCHI* (c.5A>G) in five family members affected by PD or DRD. Several arguments support the contention that this variant is pathogenic. The variant cosegregates with disease state in the family; it is absent from 300 UK control chromosomes tested here, and from all the large public databases; furthermore, it is almost completely conserved among species (Supp Fig. 2), and it is predicted to replace one of the larger hydrophilic amino acids with a small hydrophobic glycine within the N-terminal region of the protein. It is well known that in-silico prediction tools possess limited accuracy [6]. This mutation is predicted as pathogenic by SIFT and SNP&GO, but not by PolyPhen-2 and Mutation Taster. The clinical symptoms and signs observed in subjects II:1 and II:4 met diagnostic criteria for PD. In both cases the disease was more slowly progressive than is usual in idiopathic PD. Subject II:3 had an isolated rest tremor and subjects II:5, III:1 and III:11 were diagnosed with DRD. The symptoms in subjects III:1 and III:11 started at a young age and in the case of subject III:11 were more severe than those seen in subject II:5, illustrating the extreme phenotypic heterogeneity in this kindred and possibly reflecting the increased penetrance of *GCHI* mutations in females.

DaTSCAN data supported the clinical diagnoses in most cases. The clinical phenotypes of DRD and PD and correspondingly normal and abnormal scans were found in subjects carrying the same *GCHI* mutation. DAT imaging is typically normal in DRD. Indeed DAT imaging has been proposed as a diagnostic tool to help differentiate between DRD and early onset PD [5]. There have been case reports of

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individuals with adult onset dystonia-parkinsonism [7] or PD without any dystonia [8] carrying a *GCHI* mutation and an abnormal DaTSCAN.

Recently, Mencacci and colleagues reported 4 unrelated individuals with adult onset parkinsonism, presumed pathogenic *GCHI* mutations and abnormal DaTSCANs [9]. These cases, and the two in our family (subjects III:1 and III:4), raise the question as to whether PD, in patients with presumed pathogenic *GCHI* mutations, is in fact a rare phenotype of DRD. Certainly the phenotype of DRD is suggested to be broad, as illustrated by a recently reported family with classical DRD, adult onset PD and an MSA-like phenotype associated with a *GCHI* two exon deletion [3]. As recently speculated by Mencacci and colleagues [9], chronic dopamine deficiency resulting from *GCHI* deficiency could directly predispose to nigral cell death (rather than classical lewy body associated neurodegeneration as typically seen in PD). Although earlier studies screening for a *GCHI* mutations in PD cohorts did not identify a significant role for genetic variation in *GCHI*, recent studies have implicated *GCHI* as a risk locus for PD [9, 10].

An alternative, but less plausible, explanation in our family is the coincident occurrence of two separate movement disorders: a *GCHI* mutation causing DRD in some individuals an additional mutation (ie an unidentified mutation in an as yet unidentified PD gene) causing PD coincidentally in others. In those with a *GCHI* mutation and PD but no dystonia the lack of DRD phenotype could then be explained by incomplete penetrance of the *GCHI* mutation.

Olfactory dysfunction is found in 70-100% of PD patients. As DRD is a result of dopamine deficiency without neuronal cell death, we would predict that UPSIT-40

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data in DRD should be normal. In our study, the mean UPSIT-40 score for affected subjects with the *GCHI* mutation was 29.4, compared to a previous study of olfaction in PD, in which the mean score in 18 subjects with idiopathic PD was 17.1, with a score of 27.6 in 27 age-matched controls [11]. The small sample sizes which result from separating our individuals with the *GCHI* mutation limit any conclusions but the 2 individuals with PD had a mean score of 24.5 versus the 3 with DRD who had a mean score 32.7.

The DaTSCAN data for subject III:3, who had an isolated rest tremor, is difficult to explain. His first scan was abnormal, but the second scan performed 18 months later was normal. One explanation is that he suffered a vascular embolic event occurring around the time of the first scan. An alternative explanation is that there was a technical problem with one of the scans. There is also a category of subjects with parkinsonism who have normal DaTSCANS, so called SWEDDs (Scans Without Evidence of Dopaminergic Deficit), with 11-15% of subjects with PD being found to have normal nigrostriatal uptake of presynaptic ligands [12]. The novel *GCHI* mutation is not carried by subject III:3 and the most likely explanation for his symptoms is that he has isolated rest tremor due to an unrelated mechanism.

In further studies we will screen for *GCHI* variants in subjects with familial PD, and in subjects with parkinsonism who have normal DAT scans, as well as pursuing further studies into the functional effects of the novel variant described here. We anticipate that future post-mortem histological data on affected individuals, particularly those with the PD phenotype will shed more light on disease mechanisms in this interesting family.

Acknowledgements

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Author roles:

The study was designed by AJL, with support and advice by DJN, VB, and KEM. AJL and TDL carried out the clinical assessments and the LRRK2 sequencing work. SO, MQ, EJS, and VB carried out the further genetic analyses (sequencing and MLPA). EBR assessed the DaT Scans. AJL and TDL drafted the manuscript. All the co-Authors contributed to revising the manuscript for intellectual content and approved the final version for publication.

Conflict of Interest

None of the authors has any conflict of interest to disclose.

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Figure legends.

Figure 1 Pedigree of study family. Numbers refer to the age (in years) at clinical evaluation and blood sampling of the twelve family members studied.

Subject & gender	Age at eval	Age at sympt. onset	Clinical Diagnosis	L-Dopa Response	H&Y Stage	MMSE	UPSIT score (percentile)	DaT SCAN	<i>GCH1</i> mut. p.E2G
II:1 M	82	58	PD	Y	3	27	21 (40th) Severe microsmia	A	Y
II:2 M	80	N/A	Unaffected	N/A	N/A	27	31 (71st) Mild microsmia	N	N
II:3 M	78	75	Isolated rest tremor	No Rx	1	30	21 (23rd) Severe microsmia	1 A 2 N	N
II:4 M	68	50	PD	Y	2	29	28 (31st) Mod. microsmia	1 A 2 A	Y
II:5 M	66	44	DRD	Y	N/A	28	26 (24th) Mod. microsmia	N	Y
III:1 F	56	17	DRD	Y	N/A	30	35 (38th) Normosomia	N	Y
III:11 F	26	6	DRD	Y	N/A	29	37 (40th) Normosmia	N	Y

Table 1 Summary of the clinical, functional neuro-imaging and molecular genetic data on subjects from the study family. PD denotes Parkinson's disease; DRD dopa responsive dystonia; N/A not done or not appropriate; MMSE mini mental state examination score; UPSIT University of Pennsylvania Smell Identification Test; DaTSCAN dopamine transporter imaging; Mod. moderate. Age and sex corrected percentile values for UPSIT scores are presented in brackets.



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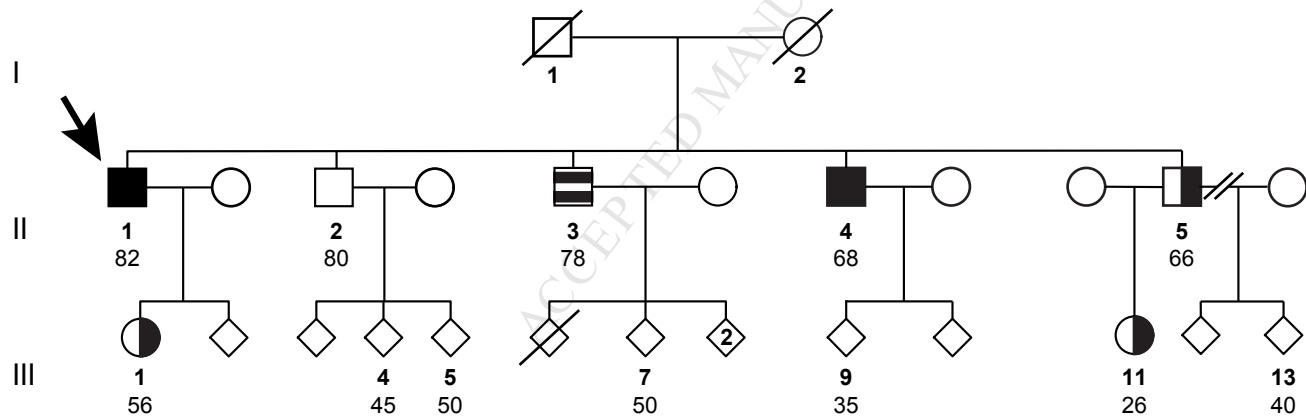
Parkinson's disease (PD)



Dopa-responsive Dystonia (DRD)



Isolated rest tremor



- We have identified a novel missense variant, c.5A>G, p.(Glu2Gly), within the *GCH1* gene in affected family members displaying a range of phenotypes including dopa responsive dystonia (DRD) and slowly progressive parkinsonism.
- Those with parkinsonism had abnormal DaTscans, indicating nigrostriatal neurodegeneration.
- These findings suggest that similar mechanisms involving abnormal GTP cyclohydrolase I may underlie both Parkinson's disease and Dopa responsive Dystonia.

Subject II:1

The proband case II:1 is a right-handed male, he was aged 82 at the time of evaluation and had onset of symptoms aged 58. His initial symptom was a resting tremor of the right hand. A diagnosis of PD was made and he was started on Levodopa (Sinemet) with significant treatment benefit. His symptoms have progressed slowly since diagnosis and his anti-parkinsonian medication has been increased.

At the time of evaluation he had had intermittent 'off-period' dystonia of the right leg for about 5 years and had also had treatment-induced dyskinesias of the right arm, as well as of the head and neck, for approximately 10 years. He did not have any significant problem with 'off-time' or fluctuations in his motor symptoms. His past medical history included hypertension as well as colon and skin cancer. He was retired and had worked as a chef for 26 years. He had never smoked and had lived most of his life in the town.

Neurological examination, on treatment, revealed features typical of PD with mask-like facies, asymmetrical rest tremor, bradykinesia and cog wheeling rigidity, all worse on the right side, as well as postural instability with retropulsion on the pull test and dyskinesias. His gait was slow with reduced arm-swing on the right side. His Hoehn and Yahr stage was 3, with a UPDRS III score of 31. The remainder of his neurological examination was normal. There was no evidence of significant cognitive deficit with a MMSE score of 27. His anti-parkinsonian medication at time of evaluation consisted of Levodopa (Sinemet) at a total daily dose of 650mg.

CT scanning of his brain, aged 84, showed cerebral atrophy, commensurate with his age.

The clinical diagnosis in this subject was a slowly progressive form of PD.

Subject II:2

He is a left-handed male, was aged 80 at the time of evaluation and was asymptomatic. His past medical history included hypertension and osteoarthritis. He was retired and had been a railway worker for 50 years. He was an ex-smoker with a 5 year pack history and had lived most of his life in the town. Neurological examination revealed no features of PD. There was no evidence of significant cognitive deficit with a MMSE score of 27.

Subject II:3

He is a right-handed male, was aged 78 at the time of evaluation and had onset of symptoms aged 75. His initial symptoms were a resting tremor of the right hand and slow gait. A diagnosis of parkinsonism was made, although his symptoms had not worsened since their onset and at the time of evaluation he had not received any anti-parkinsonian therapy. He was reported to have had two cerebrovascular accidents (CVAs); the first was at the age of 65 when he had transient balance problems and the second episode was at the age of 71, when he had developed left arm weakness and dysarthria. His past medical history included angina and atrial fibrillation. He was retired and had worked as a hairdresser for 50 years. He was an ex-smoker with a 20 year pack history and had lived most of his life in the town.

Neurological examination revealed some features of parkinsonism, with an asymmetrical rest tremor, bradykinesia and cog wheeling rigidity, all worse on the right side. His gait was slow but was within normal limits. His Hoehn and Yahr stage was 1, with a UPDRS III score of 9. The remainder of his neurological examination was normal. There was no evidence of cognitive deficit with a MMSE score of 30.

Neither a CT scan of his brain, aged 73, nor an MRI scan of his brain, aged 78, had revealed any evidence of a CVA.

The clinical diagnosis in this subject was parkinsonism as he did not meet the UKPDS brain bank diagnostic criteria for definite PD.

Subject II:4

He is a right-handed male, was aged 68 at the time of evaluation and had onset of symptoms aged 50. His initial symptoms were a resting tremor of the left hand and slow gait. A diagnosis of PD was made and he was initially commenced on Levodopa (Sinemet) 150mg daily, with significant treatment benefit. His symptoms had progressed slowly since diagnosis and were well controlled on a small dose of anti-parkinsonian medication. His past medical history included angina, hypertension and erectile dysfunction. He was retired and had worked as an exhibition designer for over 30 years. He had never smoked and had lived most of his life in the town.

Neurological examination, on treatment, revealed features suggestive of PD, namely an impassive face, asymmetrical rest tremor, bradykinesia and cog wheeling rigidity, all worse on the left side. His gait was slow and he had poor arm swing, again worse on the left side. He also had evidence of postural instability with retropulsion on the pull test. His Hoehn and Yahr stage was 2, with a UPDRS III score of 19. The remainder of neurological examination was normal. There was no evidence of significant cognitive deficit with a MMSE score of 28. His anti-parkinsonian medication at time of evaluation consisted of Levodopa (Sinemet) at a total daily dose of 150mg.

He underwent an MRI scan of his brain, aged 69, which revealed some areas of non-specific increased signal in the right lentiform nucleus and around the posterior horns of both lateral ventricles, consistent with long-standing hypertension.

The clinical diagnosis in this subject was of a slowly progressive form of PD.

Subject II:5

He is a right-handed male, was aged 66 at the time of evaluation and had onset of symptoms aged 44. His initial symptoms were a shuffling gait, difficulty with gait initiation and tremor of both legs. He was initially diagnosed with PD and commenced on a dopamine agonist (Bromocriptine) with significant treatment benefit. His symptoms progressed slowly, although Levodopa was added to his therapy six years after diagnosis, at the age of 50, to give a total daily levodopa equivalent dose of 250mg.

At the time of initial evaluation, his symptoms were well controlled on treatment. His past medical history included erectile dysfunction but was otherwise unremarkable. He was retired and had worked as retail store manager for 30 years. He had never smoked and had lived most of his life in the town. His neurological examination at this time, on treatment, appeared to be normal with no evidence of the features of PD. There was no evidence of significant cognitive deficit with a MMSE score of 28. His anti-parkinsonian medication at time of evaluation consisted of dopamine agonist (Bromocriptine) and Levodopa (Sinemet) to give a total daily levodopa equivalent dose of 250mg.

This subject was subsequently re-evaluated by Dr David Nicholl, and given a trial period of one week off anti-parkinsonian therapy. During this period his symptoms worsened, he developed a feeling of akathisia and a resting tremor of both feet. He also developed some dystonic posturing of both feet, worse on the right, which tended to be worse at the end of the day. Neurological examination at this time revealed

dystonic posturing of the right foot and resting tremor of both feet. On restarting anti-parkinsonian medication the symptoms improved. The clinical diagnosis in this subject was DRD.

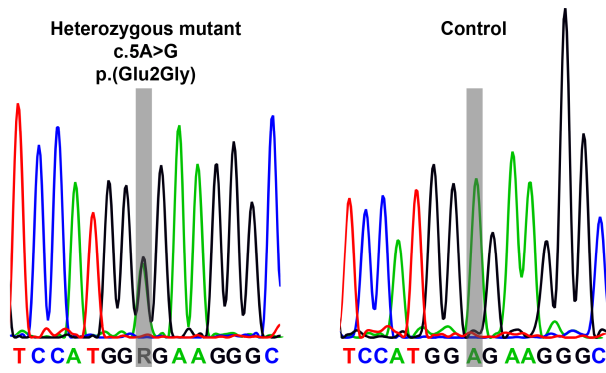
Subject III:11

She is a right-handed female, was aged 26 at the time of evaluation and had onset of symptoms aged 6. Her initial symptoms were a clawing of the toes and in-turning of the ankle of the right foot. Her symptoms progressed slowly but she subsequently developed similar symptoms of the left foot. No specific neurological diagnosis was made. At the age of 24 she developed dystonic posturing of the right hand, especially when typing or writing. All of these symptoms were worse in the evening or when stressed. Her past medical history was unremarkable. She was a secretary, had never smoked and had lived most of her life in the town.

Neurological examination at the time of evaluation, off treatment, revealed the presence of a dystonic tremor of the right hand with a tendency to claw and she developed dystonic writer's cramp whilst writing. Both feet were dystonic and were inverted. There were no other abnormal neurological features in the upper or lower limbs and allowing for the dystonic posturing of her feet her gait appeared within normal limits. There was no evidence of significant cognitive deficit with a MMSE score of 29.

She was also assessed by Dr David Nicholl and given a working diagnosis of DRD. MRI scanning of her brain revealed an apparent persistence of non-myelinated white fibres around the trigones, occipital and frontal horns. She was commenced on Levodopa (Sinemet), with significant treatment benefit, and the dose was titrated up to a total daily dose of 300mg.

The clinical diagnosis in this subject was DRD.



		E2 ↓
H. sapiens	NP_000152.1	MEKGPVRAPAEKPRGAR-CSNGFPERDPPRPGPSRPAEKPPRPE
P. troglodytes	XP_001161622.1	MEKGPVRAPAEKPRGAR-CSNGFPERDPPRPGPSRPAEKPPRPE
M. mulatta	XP_001087365.1	MEKGPVRVPAEKPRGAR-CSNGFSERDPPRPGPSRPAEKTPRPE
C. lupus	XP_005623474.1	MEKGPVRAPA-KPRGAR-CSNGFPEGEPPRPGPSGPAKPPRPE
B. taurus	XP_002690995.1	MEKGPCRVTI-TSRGAR-CSNGFLEGEPPRPGSPPAEKPPRPE
M. musculus	NP_032128.1	MEK-----PRGVR-CTNGFSERELPRPGASPPAEKSRPPE
R. norvegicus	NP_077332.1	MEK-----PRGVR-CTNGFPERELPRPGASRPAEKSRPPE
X. tropicalis	NP_001006789.1	MDPAKSR--PLLEKKAL-NCNGFLREDKKEPAAAGSRGDVGRAG
D. rerio	NP_001129727.2	MERSKQKPVNQSEKETDGAINGHFDGRVKMPGWKAGSASGDPGS

